

Combining Interferon- α 2b (IFN) and Intravenous Immunoglobulins IgG, IgM and IgA (IVIG) in Rapid Progressive Myelofibrosis (MF) With Trisomy 1

To the Editor:

Combining physiological cell-secreted molecules may impact therapeutics. Here we associate IFN and IVIG for MF after a 3-year experience with chronic hepatitis C [1].

The 59-year-old male developed 2½ years painful osteosclerosis. Two dry tap marrow biopsies bent steel needles like straw. Failing 6-month IFN-monotherapy (5 MU sc 3 times per week), transdermal fentanyl, ketorolac, and transfusions (Hb 4.4 g/dl) became necessary. Splenectomy (4 kg) only alleviated metaplasia's mechanical burden. Histology: hematopoiesis (60–65%) and fibrosis mix with hemocatheresis and scattered lymphatic tissue. Few, mostly intrasinusoidal, megakaryocytes—small and large in balance; nuclei: atypical, hyposegmented. Blood: anemia, thrombocytopenia, some immature leukocytes persisted (also tetraploid, pelgueroïd), reticulocytes fell, rising peripheral erythroblasts.

Improvement coincided with IVIG adding, (IgG: 2 g/kg) followed by IgG + IgM + IgA (14 fortnight doses, 0.4, 0.06, 0.06 g/kg [Pentaglobin, Biotech Pharma GmbH] respectively, weight adjustment, +19.5%, not done). Regularly, the patient emphasized 2–3 days postinfusion pain relief.

Thrombocytopenia already recovered in 30 days (30 to $289 \times 10^9/L$, some macroplatelets), ESR somewhat slower (140 to 13 mm), anemia that remained at decompensation's edge, hints to revert (9 g/dl). WBC-counts, throughout normal; blasts fell from 8% to admission values. After 14 months of the combined treatment, the patient feels well without opioid support. Two marrow biopsies from the same iliac spine as before, now spongiosa-like, respectively, harvested blood and 5 ml of cell-rich hematopoietic material (karyotype: 47,XY,+1). While trabeculae expanded, osteosclerosis is less evident. Liver, echostructurally normal, is slightly enlarged; enzymes initially increased, normalized, but protein patterns and hypocholesterolemia (3.3 mmol/l) suggest incipient cirrhosis (biopsy not done). Serum lactic dehydrogenase (LDH) remains high, uricemia normal.

Cytopenia evolved overshadowed by deterioration and weight loss. No metaplastic bulk was found, liver enlargement being negligible, and cirrhotic shrinkage unlikely. Peripheral blood values favor fibrotic and osseous reaction's reversal, hematopoiesis repopulating its natural environment.

In MF, a clonal proliferative disorder with abnormal stem cell behavior [2], Trisomy 1 is rather uncommon. Usually secondary manifestations determine the clinical picture. The hallmark fibrosis, often osteosclerosis, depends on a complex fibroblast-megakaryocyte interaction [2]. Presumably, platelet-granules release excessive platelet derived growth factor (PDGF) increasing serum levels [3]. Thrombocytes, sometimes excessive, paradoxically also can be scarce with bleeding risk, we only saw few megakaryocytes. Evidence of malignancy intermingled with immune, cytokine, and other networks involved is on the rise. In MF may coexist a wide range of autoimmune phenomena.

When marrow transplantation is no option, therapy remains elusive. Splenectomy may correct hemocatheresis, but there was no rebound. Occasional IFN benefit is poorly understood and unrelated with rare cytogenic responses. It may prolong survival and reduce splenomegaly (actually the opposite happened). Fibrosis expands or shrinks suggesting conversely acting mechanisms. IFN-failure here suggests that IVIG's role was not neutralization of IFN-induced antibodies, but rather to dampen factors tending to perpetuate disease, even promoting malignancy. The chosen preparation contains IgG, IgA, IgM isotypes, perhaps contaminants as well.

You may ask, why not pooled plasma? We think it is a good question, but it would not allow us to retain the high-dose concept. Although clonality and leukemic risks persist, targeting reactional manifestations seems important.

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Hemophagocytosis by Rhabdomyosarcoma Cells in Bone Marrow

To the Editor: Hemophagocytosis is a hallmark of malignant histiocytosis, and is not uncommon in other malignant hematological entities such as prolymphocytic leukemia, acute lymphoblastic leukemia, acute erythroleukemia lymphomas, multiple myeloma, myelodysplastic syndrome, and, especially, acute monocytic leukemia. Its occurrence in non-hematological malignancies is rare, represented by single-case reports of small cell lung carcinoma [1], undifferentiated lung carcinoma [2], breast carcinoma [3], medulloblastoma [4], and hemangioendotheliosarcoma [5]. We now describe a heretofore unreported finding of hemophagocytosis by rhabdomyosarcoma cells in the bone marrow.

A 14-year-old girl had numerous prolonged symptoms before she sought medical advice. Six months prior, she developed bilateral painless firm enlargement of her breasts. One month prior, she noticed an enlarging mass at the thenar region of the left hand. She also had many episodes of unprovoked epistaxis. Two weeks prior to admission, she suffered from easy fatigue and dizziness. The past history was unremarkable. Physical examination revealed severe pallor, petechiae over the face and limbs, and multiple firm lymph nodes in both axillary regions. Fundal hemorrhage

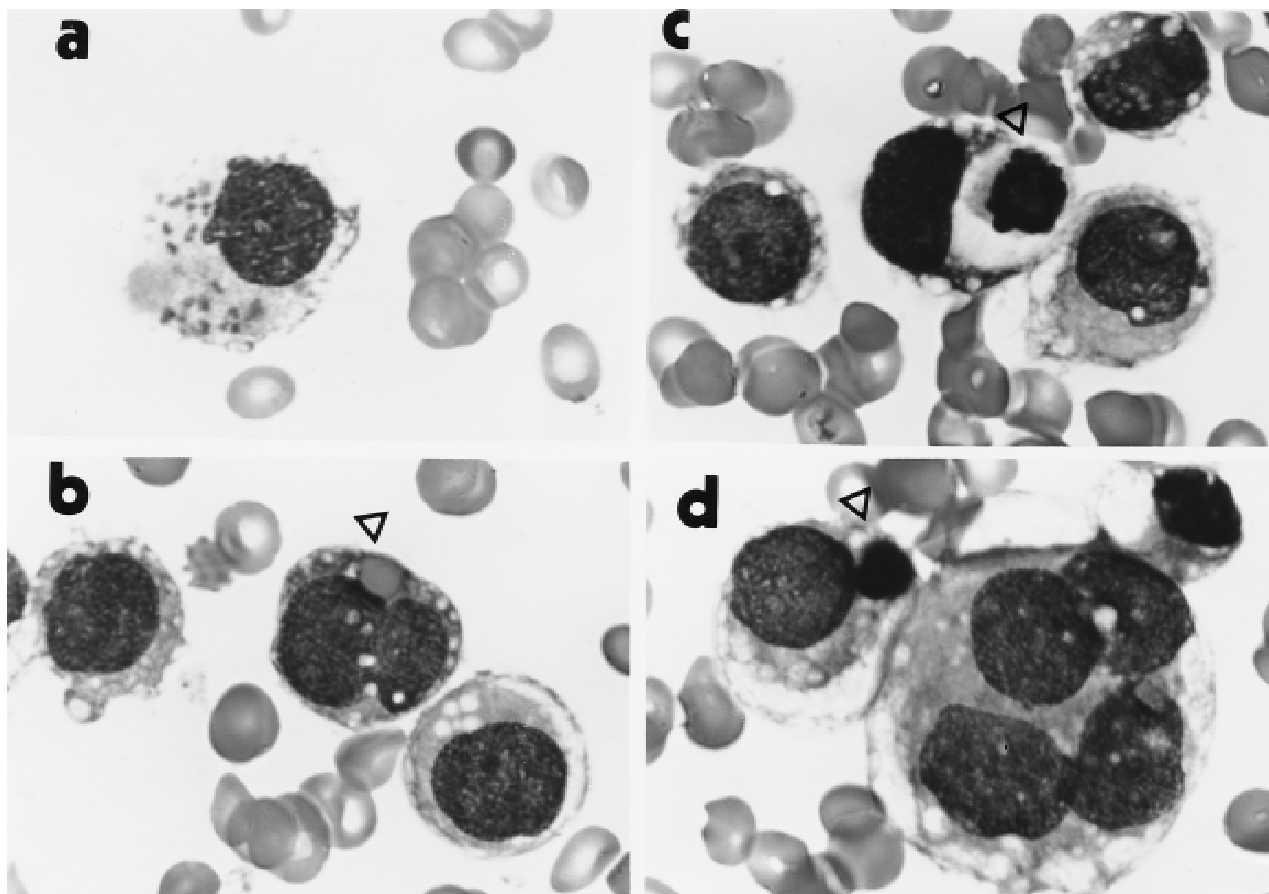


Fig. 1: a: Tumor cells with many ingested platelets. b: Binucleated tumor cell with phagocytised erythrocyte (arrowhead). c: Tumor cell with phagocytised leucocyte (arrowhead). d: One multinucleated tumor cell, next to a tumor cell with phagocytised leucocyte (arrowhead). Magnification: $\times 1,000$.

was detected in the left eye. A mildly tender mass measuring 3 cm in diameter was found at the left thenar region. Both breasts were similarly affected; each fully occupied by a mass with a nodular surface and irregular edges, and fixed to the underlying tissue.

Bone marrow smear showed that over 90% of marrow cells were tumor cells. They were characterized by vacuolated cytoplasm, and the propensity to form pairs, clusters, and multi-nucleated forms. Phagocytosis of erythrocytes, leucocytes, and platelets was rampant (see Fig. 1). Trephine biopsy showed almost complete replacement of marrow by small round cells, which stained positively for actin, desmin, and vimentin, but negatively for LCA and cytokeratin. The diagnosis of rhabdomyosarcoma (alveolar type) was established.

After a course of induction chemotherapy consisting of vincristine, adriamycin, and cyclophosphamide, the patient underwent bilateral simple mastectomy followed by radiotherapy to chest wall and left hand. Intensive consolidation chemotherapy consisting of carboplatin and melphalan was then administered, in conjunction with autologous peripheral blood stem cell transplantation. The patient thereafter enjoyed a 4-month disease-free period until the sudden recurrence of severe pancytopenia and bone marrow examination revealed extensive infiltration of the marrow by metastatic rhabdomyosarcoma cells showing again active hemophagocytosis. CT scan of brain revealed intracranial hemorrhage. The patient died shortly after.

This case demonstrates hemophagocytosis by alveolar rhabdomyosarcoma, and adds to the growing list of non-hematological malignant cells showing phagocytic ability. We cannot offer any clue to the basic mecha-

nism and pathophysiology of this unusual behavior of a solid tumor. According to the literature [3], purported causes include intratumoral hemorrhage and cytotoxic drug therapy. We do not think either of these causes likely, because while both intratumoral hemorrhage and chemotherapy are common, hemophagocytosis is extremely rare. Intratumoral hemorrhage may confer availability of blood cells rather than physiological changes of the cells involved—hence hemophagocytosis is more frequently described in the marrow [1,2,4]. It is also unlikely that chemotherapy is a prerequisite because hemophagocytosis has been described before the start of chemotherapy [3]. The present case supports the above arguments. Hemophagocytosis by tumor cells was found in the marrow, and it occurred both before and after chemotherapy.

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Severe Autoimmune Hemolytic Anemia Following Fludarabine Therapy in a Patient With Chronic Lymphocytic Leukemia

To the Editor: A common complication of chronic lymphocytic leukemia (CLL), autoimmune hemolytic anemia (AIHA), occurs in 10–25% of patients [1]. The cause of AIHA remains unknown. Fludarabine (9-B-D-arabinofuranosyl-2-fluoradenine), which is a potent inhibitor of adenosine deaminase, may be the therapy of choice for previously unsuccessfully treated Rai's Stage III and IV CLL patients [2]. Major side effects such as myelosuppression and infections have been attributed to fludarabine, and in higher doses it may cause central nervous system toxicity as well as pulmonary toxicity [1,2]. We describe a CLL patient who developed AIHA after fludarabine therapy.

A 65-year-old male with CLL (Rai Stage IV), who did not respond to chlorambucil and prednisolone therapy or to COP (cyclophosphamide, oncovin, and prednisolone), received fludarabine therapy (25 mg/m²/5 days/month). At the beginning of fludarabine therapy the patient had WBC = $130 \times 10^9/L$ with lymphocytes 99%, neutrophils 1%, and platelets $30 \times 10^9/L$. A direct Coomb's test was negative.

Following three cycles of fludarabine therapy the patient developed severe autoimmune hemolytic anemia. Laboratory examination showed Hb = 5 mg/dl, LDH = 1,879 IU/liter, bilirubin = 3 mg/L, and a positive Coombs test as follows: anti IgG positive +++, anti IgA (–), anti IgM +, anti C_{3c}(–), anti C_{ed} +++. As treatment for autoimmune hemolytic anemia, prednisolone therapy (1 mg/kg/day) was administered and the anemia improved.

Autoimmune phenomena do not seem to be a risk factor in CLL patients although AIHA usually occurs in more advanced or progressive disease [1]. The pathogenesis of autoimmune phenomena in CLL remains unknown. Antibodies against red cells have been reported in CLL as well as in patients with most types of lymphoid tumors [3]. The prevalence of such antibodies in CLL ranges between 7.7 and 35% [1]. Hemolysis in CLL has also been reported when conventional therapies such as leukeran and radiotherapy have been used [1].

Sporadic cases of CLL patients who developed AIHA following fludarabine therapy have been described in the literature [1,4].

Fludarabine therapy decreases all populations of lymphocytes and especially CD4⁺ cells. This effect probably contributes to the development of opportunist infections and may play an important role in AIHA occurrence. Fludarabine may cause severe autoimmune hemolytic anemia in CLL patients with a positive Coombs test as well as in those whose Coombs test is negative [2].

Usually CLL patients are elderly with decreased thymic function and a decreased number of autoregulatory T cells. For this reason, elderly CLL patients who have received fludarabine therapy appear to be at an increased risk of autoimmune disturbances [4,5].

The first hemolytic complication that arises from fludarabine therapy may be corrected with high dose prednisolone (1 mg/kg/day) but a second hemolytic episode is very difficult to resolve.

Although fludarabine treatment may cause AIHA in CLL patients, this complication does not worsen the prognosis of CLL.

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Nondeletional α -Thalassemia in a Spanish Population

To the Editor: We read with interest the article entitled "Nondeletional α -Thalassemia: First Description of $\alpha^{Hph}\alpha$ and $\alpha^{Nco}\alpha$ Mutations in a Spanish Population" by Ayala et al. [1]. The authors report ten families with nondeletional forms of α -thalassemia, nine (fifteen cases) with $\alpha\alpha/\alpha^{Hph}\alpha$, and one family with $\alpha\alpha/\alpha^{Nco}\alpha$ mutation.

In relation to this, in a study of 536 cases of α -thalassemia studied from 1990 to 1996, we found 16 cases (nine families) with nondeletional α -thalassemia, ten cases (five families) with IVS I splice junction mutation with the α_2 gene, five (four families) with a mutation of the initiation codon of the α_1 gene, and finally a single patient with the homozygote state for the initiation codon mutation of the α_1 gene [2,3]. The molecular studies were performed using DNA restriction analysis by the Southern blot method [4]. All patients were studied with the restriction enzymes *Bam*HI, *Bg*II, *Eco*RI hybridized with 1.5 Kb *Pst*I α probe and 1.8 Kb *Sac*I ζ probe, and *Nco*I, *Hph*I hybridized with α probe.

Ten patients showed a 1.4 Kb abnormal band in addition to the 1.2, 1.1, and 0.3 Kb normal bands, which demonstrates that these patients are heterozygous carriers of the 5 bp deletion at the donor site of IVS I of the α_2 -globin gene. The pentanucleotide deletion (TGAGG) removes recognition sites of the *Hph*I enzyme, located within the splice junction of IVS I ($\alpha\alpha/\alpha^{Hph}\alpha$) [5]. In these patients, the microcytosis is more severe than that corresponding to the heterozygous α^+ thalassemia (Hb 12.5 g/dl \pm 0.9, VH 36.6% \pm 2, VCM 69 fl \pm 4, HCM 23 pg \pm 1.5). The globin chain synthesis was determined in five patients and showed an α/β ratio of 0.7 \pm 0.13.

In five patients the digestion of the DNA with the restriction enzyme *Nco*I and hybridization with α probe showed an 8.5 Kb abnormal band in addition to the 4.8, 3.7, and 2.1 Kb normal bands. The abnormal band is

produced by the abolition of the recognition sites of the *NcoI* endonuclease located in the 5' part of the α_1 gene and replaces the normal 3.7 and 4.8 Kb fragments [6]. A single patient showed two bands of 8.5 and 2.1 Kb which prove that this patient is homozygous for the initiation codon mutant of the α_1 gene ($\alpha\alpha^{Nco}/\alpha\alpha^{Nco}$). We did not find any patient with the mutation in the initiation codon of the α_2 gene ($\alpha\alpha/\alpha\alpha^{Nco}$).

According to our studies the presence of nondeletional α thalassemia is estimated to be 2.93%, similar to the results of Ayala et al. [1].

Our patients came from Castilla La Mancha, Extremadura, Valencia, and Andalucía, and this fact suggests that the incidence of α -thalassemia is homogeneously distributed in all areas of Spain.

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peritoneal adenopathy and involvement of lymphoma in liver, stomach, and intestine. An initial bone marrow aspirate and biopsy showed complete trilineage maturation with no evidence of Hodgkin's disease. In December 1992, she developed severe generalized weakness, ptosis, diplopia, and dysphagia following one course of chemotherapy with MOPP/ABV. Laboratory data included an acetylcholine receptor antibody (AChR Ab) titer of 28 nmol/l (normal, <0.5) and negative antistriated muscle antibody. Repetitive stimulation studies of facial and spinal accessory nerves were reported to be normal. At that time, the patient was anemic with normal white cell and platelet count. There was no evidence of gastrointestinal bleeding. A bone marrow aspirate and biopsy revealed a cellular marrow with normal myelopoiesis and megakaryopoiesis and with severe decrease of erythroid precursor cells (<3%). Combination of immunoabsorbance therapy, steroid, and pyridostigmine was effective for treatment of MG. In addition, she experienced a steady resolution of her PRCA. Two weeks after additional cycle of MOPP/ABV, the patient became acutely ill with fever and pneumonia. Although she was treated with various antibiotics, she did not recover.

Our case suggests that the MOPP/ABV therapy and/or Hodgkin's disease induced immunoregulatory disturbance, allowing the emergence of autoreactive erythroid suppressor T cells and of AChR Ab. This improvement results from aggressive immunosuppressive therapy. To our knowledge, there have been no cases described in the literature in which MG and PRCA are concomitant associations with Hodgkin's disease.

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Concomitant Association of Myasthenia Gravis and Pure Red Cell Aplasia After Chemotherapy for Hodgkin's Disease

To the Editor: Myasthenia gravis (MG) is an autoimmune disease associated with increased frequency of thymic malignancy. There are reports suggesting a relationship between MG and lymphoma [1–3]. Association of pure red cell aplasia (PRCA) with Hodgkin's disease is rare, with only six previously reported cases in which PRCA preceded or was concomitant with the diagnosis of Hodgkin's disease [4]. We report here a unique case of concomitant association of MG and PRCA after chemotherapy for the stage IVB mixed cellularity Hodgkin's disease.

A 37-year-old Japanese woman with Hodgkin's disease (mixed cellularity) was first admitted for treatment of the disease in November 1982 at the age of 24. She received only radiation therapy at the diagnosis and refused any further treatment for 13 years. Staging evaluations including CT of the chest and abdomen revealed bilateral hilar and massive retro-

Siliconized Glass Versus Polypropylene To Reduce In Vitro Platelet Activation

To the Editor:

In vivo platelet activation is difficult to assess because even the slightest in vitro stimulation creates artifacts in collected blood samples [1]. Kuhne et al., however, reported the successful use of the Diatube-H (Diagnostica Stago, Asnieres, France) in collecting blood for flow cytometric evaluation of platelet activation [2]. We have also used this tube successfully to collect samples for measurement of platelet factor-4 (PF4) in plasma (Asserachrom PF4, Diagnostica Stago). Recently, however, the Diatube-H was removed from the market.

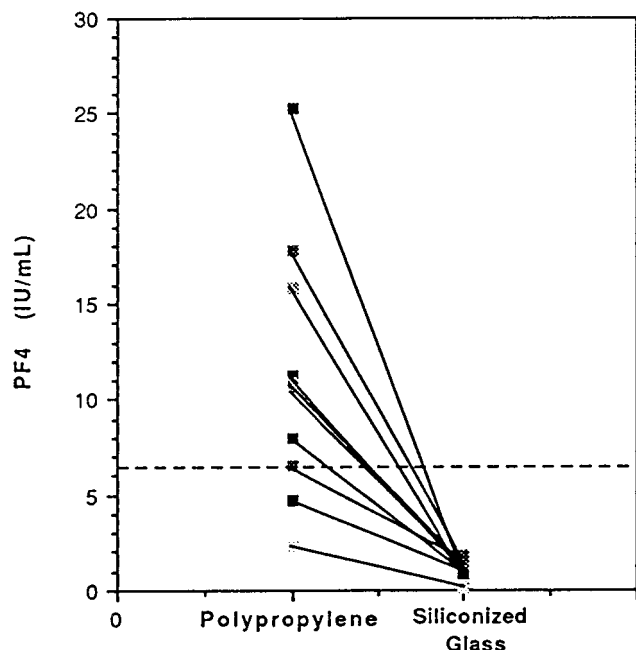


Fig. 1. PF4 measurements for plasma samples from 10 normal donors, collected in C.T.A.D., either in polypropylene tubes or siliconized glass tubes. Solid lines connect results for the same individual generated from the same run. The dashed line indicates the upper limit of normal PF4 concentration.

To replace the siliconized glass Diatube-H we used polypropylene tubes containing exactly the same mixture of anticoagulant and platelet inhibitors (0.11 M citrate, 15 mM theophylline, 3.7 mM adenosine, 0.198 mM dipyridamole [3]). Unfortunately blood samples collected in the polypropylene tubes from normal donors consistently showed elevated levels of PF4. Adding the anticoagulant mixture to siliconized glass tubes (Becton Dickinson, San Jose, CA; buffered sodium citrate tubes, rinsed with deionized water and air-dried), however, eliminated the problem (Fig. 1).

This observation was very unexpected since polypropylene is generally considered not to activate platelets and, in fact, has been the material we have used for many years when collecting samples for platelet function studies [1]. It appears, however, that siliconized glass is less stimulating than polypropylene and may be another factor critical in preventing in vitro platelet activation.

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Allogeneic Bone Marrow Transplantation for a Patient Complicated by Chronic Hepatitis Due to Precore Mutant Hepatitis B Virus: Failure of Management With Interferon- α Therapy

To the Editor: Hepatitis B surface antigen (HBsAg) positivity is reportedly not a risk factor for the failure of bone marrow transplantation (BMT). When the hepatitis B virus is a precore mutant, its effect on the outcome of BMT may be different [1].

A 44-year-old man with acute myelomonocytic leukemia (AMMoL) in second remission underwent BMT from an HLA-identical sister. He had suffered from chronic hepatitis due to precore mutant hepatitis B virus (HBV) prior to transplantation. Although the serum concentration of HBV-DNA polymerase (DNA-P) rose prior to preconditioning, interferon- α (IFN- α) administration, 600 mega-units for 15 days, reduced its level from 2,750 cpm to 1,348 cpm, and liver function tests were normal at marrow infusion. A serum concentration of DNA-P began to rise again on day 7 after BMT (Fig. 1). IFN- α , 600 mega-units, was initiated again from day 14. Since a DNA-P level decreased from 3,312 cpm to 1,673 cpm, the dose of IFN- α was reduced to 300 mega-units on day 28. On the same day, erythematous, macropapular eruptions appeared on the neck and upper extremities. On day 30, the erythema extended to the trunk and lower extremity, leaving less than 50% skin area. Skin biopsy showed acute graft-versus-host disease (GVHD), stage III. Although prednisolone, 60 mg/day, was administered orally from day 30, diarrhea and jaundice appeared on day 32 and exacerbated despite the cessation of IFN- α and administration of high-dose methylprednisolone. The serum DNA-P concentration began to increase on day 28, reaching 7,312 cpm on day 42. The patient ultimately died of liver failure due to hepatic GVHD on day 65.

This patient was at high risk of developing fulminant hepatitis following high-dose radio- and chemotherapy. However, since the patient was in second remission of AMMoL, allogeneic BMT was thought to be the only curative treatment. IFN- α was reportedly effective in preventing reactivation of precore mutant HBV [2]. Moreover, the administration of IFN- α before BMT appeared to be effective in suppressing viral replication in this patient. The patient, therefore, proceeded to allogeneic BMT following high-dose radio- and chemotherapy. Mayers et al. [3] reported that the administration of IFN- α to allogeneic marrow transplant recipients was not associated with increased incidence or higher grade of GVHD. On the other hand, IFN- α has been used to induce GVHD for patients with relapsed hematologic malignancies [4]. Severe acute GVHD (greater than grade III) is rare in Japanese patients grafted with marrow from HLA-identical sibling donors [5]. Thus, the administration of IFN- α early after BMT seemed to be responsible for the development of severe GVHD in this patient. The clinical course of this patient indicates that the use of IFN- α may not be beneficial to allogeneic marrow transplant recipients with chronic hepatitis due to precore mutant HBV, but it also may induce fatal GVHD. When BMT is planned for a patient carrying precore mutant HBV, a prophylactic antiviral treatment other than IFN- α , such as HB immunoglobulin, should be considered.

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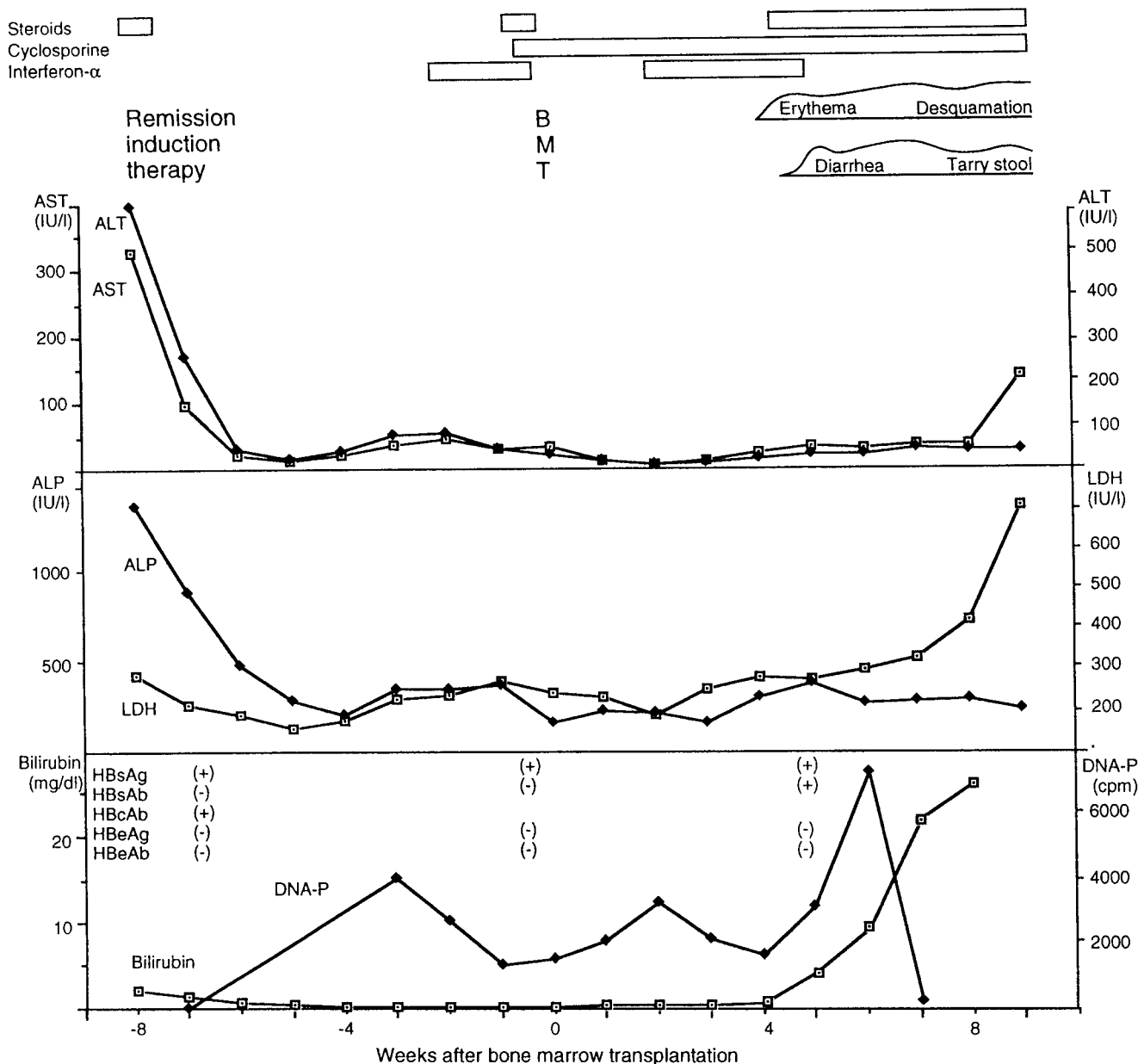


Fig. 1. Changes in results of liver function tests before and after BMT.

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Clozaril-Induced Lupus Anticoagulant

To the Editor: Lupus anticoagulants are immunoglobulins, usually IgG or IgM, named after being first recognized in a patient with systemic lupus

erythematosis (SLE). It is a misnomer, as it often occurs in patients who do not have SLE. We report an unusual finding of this anticoagulant and abnormal activated partial thromboplastin time (aPTT) in a patient taking clozapine (Clozaril).

A 39-year old Caucasian male with chronic schizoaffective disorder was referred for an abnormal aPTT. He had a 5-week history of constipation that was not relieved by a stool softener (Colace). He consulted his primary care physician. A hemocult test was positive. He underwent sigmoidoscopy, which revealed a single diverticulum. Repeat hemocult tests were persistently positive. Prothrombin time (PT) and aPTT were done prior to a possible colonoscopy, showing a PT of 13 sec (control = 12.1 sec) and aPTT of 34.2 sec (control = 27 sec). A hematology consultation was sought at this point. The patient's past medical history was significant for recurrent hospitalization due to schizophrenia. He has been treated with a different antipsychotic medications and lithium. Because of an apparent lack of improvement with traditional antipsychotic medications, thioixithene hydrochloride (Navane) and lithium were discontinued about 1 year ago. Instead, Clozaril was started in the hope of bringing about significant improvement. The initial dose of Clozaril was 225 mg/day. His other medication, carbamazepine (Tegretol) was stopped at about the same time. At the time of the hematology consultation, his medications were Clozaril, Klonopin, Cogentin, and Lopid. Laboratory findings showed a normal CBC, aPTT 36 sec (control 28.0 sec), PT 14 sec (control = 12 sec), TT 21 sec (control = 19 sec), and negative ANA titer. The lupus anticoagulant test (by tissue thromboplastin inhibition test) was positive. Anticardiolipin and antiphospholipid tests were negative.

DISCUSSION

This patient has a positive lupus anticoagulant, which is the probable cause of his abnormal aPTT. This case illustrates a probable etiologic relationship between Clozaril and the lupus anticoagulant. Considering the above clinical history, medication history, unremarkable physical examination, and

duration of abnormal coagulation tests, it can be deduced that this patient's prolonged aPTT and positive lupus anticoagulant were secondary to Clozaril. Drugs, particularly phenothiazine, are known to cause a positive lupus anticoagulant test. A probable drug-induced etiology was considered in this case. The patient was not receiving phenothiazines, but a related antipsychotic medication, Clozaril. Clozaril was the only new drug he had been taking. Clozaril has been known to cause agranulocytosis; however, there are no reports on Clozaril-induced lupus anticoagulant. It was much harder to pinpoint another drug. Comparison of chemical structures showed a central ring structure similarity to the phenothiazines, which have long been associated with a drug-induced lupus anticoagulant. Patients with drug-induced lupus anticoagulants do not exhibit clinical evidence of thrombosis. These patients do not require anticoagulation. We inferred that this patient has prolonged aPTT secondary to lupus anticoagulant associated with the intake of Clozaril.

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